

REMARKS/ARGUMENTS

Interview

Applicants appreciate the opportunity to discuss the Office Action with Examiners Brooks and Richter on July 31, 2008. Applicants' attorney presented a central argument against the obviousness rejection, namely, that none of the cited references link interferon-alpha to glucocorticoid dysregulation, and that one of skill would therefore not reasonably expect a glucocorticoid receptor antagonist to address the psychotic side effects of interferon-alpha therapy. Applicant also explained that "psychiatric conditions," generally, and "depression" in particular, do not necessarily indicate psychotic symptoms. These arguments are presented in detail below. The Examiners indicated that they would consider the arguments upon receipt of the response.

Status of the claims

Claims 1-4 and 8-19 remain pending. Claim 17 is amended to correct a minor grammatical error. No new matter is added.

Rejection under 35 USC § 103: Schatzberg in view of Ademmer

The Examiner has rejected claims 1-4 and 8-17 as allegedly obvious over Schatzberg (U.S. Patent No. 6150349) in view of Ademmer (Psychosomatics 42:365-67 (2001)). More specifically, the Examiner asserts that Schatzberg teaches methods of ameliorating psychosis- psychotic major depression in particular- using a glucocorticoid receptor antagonist (GRA). The Examiner notes that psychosis is defined to include psychiatric conditions or symptoms associated with, *e.g.*, a side effect of medication. *See* Office Action, page 5. The Examiner states that Ademmer teaches that IFN- α treatment of HCV patients often results in depression and suicidal ideation. *See* Office Action, page 6. According to the Examiner, it would be obvious to treat the symptom of psychosis associated with IFN- α , as taught by Ademmer, using the GRA taught by Schatzberg. *See* Office Action, page 7.

In response to Applicants' arguments in the October 3, 2007 Amendment, the Examiner emphasizes that Schatzberg defines psychosis broadly as a condition that can result as a side effect of medication. According to the Examiner, the methods of Schatzberg apply equally to psychosis as an illness itself or as a symptom resulting from medication. *See* Office Action, page 9.

Applicants respectfully traverse the rejection. Applicants will explain that Schatzberg, while providing a broad definition of psychosis, clearly limits the scope of the invention to psychotic symptoms caused by glucocorticoid dysregulation. Neither Schatzberg nor Ademmer suggest that IFN- α has any effect on glucocorticoid signaling or regulation. A skilled artisan would therefore have no reason to expect that IFN- α related psychosis would respond to GRAs.

As an initial matter, Ademmer does not discuss psychosis related to IFN- α , but describes a patient with IFN- α related depression. Applicants concede, however, that the contemporary art disclosed that IFN- α can cause psychotic symptoms in a small subpopulation of patients. US Patent Publ. 20030180719 (December 3, 2002 priority date) states that contraindications of IFN include psychosis (*see* paragraph 5). US Patent Publ. 20050032849 (July 10, 2003 priority date) states that side effects of IFN- α include acute psychosis (*see* paragraph 11).

Despite the fact that the psychotic side effects of IFN- α therapy were known, the Examiner has not shown that one of skill in diagnosing and treating psychological disorders would reasonably expect that a GRA would successfully treat the **particular** psychoses related to IFN- α treatment. Thus, the Examiner has therefore not presented a proper *prima facie* case of obviousness. This argument is explained in more detail below.

Legal standard

Section 2142 of MPEP sets forth the three criteria that the Examiner must meet to establish a *prima facie* case of obviousness.

First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The Supreme Court in *KSR* warned against overly rigid application of the so-called teaching/ suggestion/ motivation (TSM) test of obviousness and essentially expanded the field of knowledge from which a motivation to modify or combine the references could be drawn. The motivation to combine may be explicit or implicit and may be found in the knowledge of one of ordinary skill in the art, scientific principles, or legal precedent. *See* MPEP § 2144. However, the Examiner must still establish that one of skill in the art would have a reasonable expectation of success in making the claimed invention. *See* MPEP § 2143.02.

The invention

The present invention is based on the discovery that blocking the effect of cortisol on glucocorticoid receptor signaling reduces the psychotic symptoms of patients undergoing IFN- α therapy for unrelated conditions. Thus, the invention provides a method of ameliorating the serious mental side effects of interferon-alpha (IFN- α) therapy by blocking the effect of cortisol on GR signaling with a GR antagonist (GRA).

Ademmer discusses depression related to IFN- α therapy, not psychosis

Ademmer does not relate to the patient group targeted by the present invention, *i.e.*, patients undergoing IFN- α therapy that develop psychotic symptoms. Ademmer states that serious side effects of IFN- α therapy include "psychiatric symptoms, particularly depression and suicidal ideation." The reference does not disclose that psychotic symptoms are included in the psychiatric symptoms experienced by IFN- α patients. The article focuses on the experience of one patient with major depression. Thus, Ademmer does not effectively teach that IFN- α is related to psychotic symptoms, as distinguished from psychiatric symptoms broadly, or depression in particular.

As noted above, the art from the time does disclose psychotic symptoms arising in patients undergoing IFN- α therapy. *See, e.g.*, US 20030180719 and US 20050032849. Despite

this, one of skill would still not expect the anti-psychotic taught by Schatzberg to effectively address psychotic symptoms resulting from IFN- α therapy, because there was no known correlation between IFN- α and glucocorticoid dysregulation. The reason is explained in detail below.

A person of skill would recognize that psychotic symptoms have distinct etiologies

A small subset of patients undergoing IFN- α therapy suffer from psychotic symptoms. Psychotic symptoms, however, can result from a number of different causes, *e.g.*, post traumatic stress disorder, schizophrenia, schizoaffective disorder, fever, and delirium. A similar example is high blood pressure, which may arise in individuals with kidney malfunction, diabetes, excessive stress, or atherosclerosis. A medical professional would not use the same therapeutic approach for all four of these patients simply because they share a symptom. Similarly, a psychiatric professional would appreciate the complexity of mental disorders, their causes, and therapeutic approaches. The Examiner has not shown why the skilled practitioner would expect to successfully apply the same approach to address psychosis in diverse patients.

In the October 9, 2007 response, Applicants explained that psychosis is a symptom of a disease, and not a disease in and of itself. The Examiner has acknowledged this argument, but has maintained Schatzberg as a reference because it defines psychosis broadly to include conditions related to the side effect of medication.

Applicants respectfully contend that one of skill at the time the present application was filed would understand that treatment of psychotic symptoms arising from different etiologies should be approached differently. The Examiner has not shown why a skilled artisan would expect a drug that effectively treats psychosis associated with glucocorticoid dysregulation, *e.g.*, a GRA, to be useful for psychotic symptoms arising from other causes.

Schatzberg teaches that not all psychoses can be treated according to its methods

Schatzberg provides medically accepted definitions of "psychotic" and "psychosis." However, Schatzberg does not imply that all psychoses can be treated according to their disclosed methods. Schatzberg only states that psychoses arising from defective glucocorticoid pathways can be treated using a GRA. Thus, while Schatzberg broadly defines

conditions with psychotic features, the utility of the invention is clearly limited. And as explained below, Schatzberg does not disclose that IFN- α affects glucocorticoid regulation.

Schatzberg (col. 5, lines 57-61) discusses psychotic symptoms associated with schizoaffective disorder. The disclosure continues to explain that schizophrenia-associated psychoses are not usually caused by dysfunctions in glucocorticoid regulation. *See* Schatzberg, col. 6, lines 61-67. Schatzberg then explains that these disorders are not treated by the methods of the invention. *See* Schatzberg, col. 7, lines 10-11.

After the Schatzberg disclosure was written, the inventors assembled data demonstrating that psychoses arising from different etiologies could not be treated identically. In 1999, the inventors submitted data from clinical trials to the FDA. Their studies were carried out determine the safety and efficacy of a GRA (mifepristone) in treating psychosis in patients suffering from either psychotic major depression or schizoaffective disease. The results indicated that, while mifepristone ameliorated symptoms of PMD, it had little effect on patients with schizoaffective disease.

Dr. Joseph Belanoff, the inventor of the present invention, submitted a Declaration explaining these results during prosecution of the Schatzberg patent. *See Exhibit A*, which includes the Declaration and Exhibit 1. The Declaration explains that the methods described in that disclosure are not applicable to all types of psychotic symptoms. *See Ex. A*, paragraphs 5 and 7. As explained in paragraph 7 of the Declaration, mifepristone treatment did not ameliorate the symptoms of schizoaffective patients.

The Examiner has not demonstrated why one of skill at the time of the present invention would understand Schatzberg to mean that GRAs are effective for ameliorating psychotic symptoms arising from any cause. Schatzberg explains that only those psychoses arising from dysfunction in glucocorticoid regulation are targeted by their methods. Data submitted during prosecution of that patent provide further evidence of this point.

Neither Schatzberg nor Ademmer link IFN- α to glucocorticoid signaling

A psychiatric professional would not relate glucocorticoid dysregulation to IFN- α , given Schatzberg, Ademmer, and the knowledge in the art at the time. Schatzberg does not

suggest that IFN- α has any effect on glucocorticoid regulation. Ademmer does not cure this defect. Applicants are not aware of any information that would lead one of skill, faced with a patient undergoing IFN- α therapy and showing signs of psychotic symptoms, to expect a therapy designed to address dysregulation of glucocorticoid signaling to ameliorate the side effect of IFN- α .

Conclusion

The Examiner has not met the burden of establishing a *prima facie* case of obviousness. There is no evidence that a person of skill would have any reason to expect that the GRA therapy taught by Schatzberg would effectively ameliorate psychotic symptoms associated with IFN- α therapy. Schatzberg explains that GRAs are effective in treating psychotic symptoms associated with defects in glucocorticoid regulation, and does not link IFN- α to glucocorticoid dysfunction. Ademmer discloses that IFN- α results in depression, not psychosis, and does not link glucocorticoid regulation to either. Unless the Examiner can identify prior art disclosing that IFN- α therapy is linked to glucocorticoid dysregulation, Applicants respectfully request withdrawal of the rejection under 35 USC § 103.

Rejection under 35 USC § 103: Schatzberg in view of Ademmer and Dieterich

The Examiner has rejected claims 18 and 19 as allegedly obvious over the same references, in further view of Dieterich (2002) *J. Infectious Diseases* 185(Suppl 2):S128-137. According to the Examiner, Dieterich teaches that coinfection of HCV and HIV is common, especially among intravenous drug users. See Office Action, page 10. The Examiner asserts that Dieterich also states that IFN- α and ribavirin can lead to neuropsychiatric effects including depression, anxiety, personality change, etc. See Office Action, page 11.

Applicants respectfully traverse the rejection because Dieterich does not suggest a connection between IFN- α and glucocorticoid regulation, and therefore does not cure the defect of Schatzberg and Ademmer. Applicants also note that Dieterich, like Ademmer, fails to teach the patient group targeted by the present invention. As explained above, however, Applicants are aware that the art disclosed psychotic symptoms appearing in a subset of IFN- α recipients.

Like Schatzberg and Ademmer, Dieterich fails to link IFN- α to glucocorticoid regulation. The reference discloses a number of different side effects of ribavirin and IFN- α combination therapy, including hepatotoxicity, anemia, flu-like symptoms, neuropsychiatric effects, gastrointestinal symptoms, and fatigue. *See* Dieterich, pages S132 and S134. Dieterich even suggests approaches to counteract these side effects, none of which include GRAs or any glucocorticoid-related therapy. *See* Dieterich, Figure 5.

Moreover, Dieterich, like Ademmer, fails to make any mention of psychotic symptoms resulting from IFN- α therapy. The present invention targets the subset of patients undergoing IFN- α therapy that develop psychotic symptoms. Claim 18 further limits the patient group to individuals suffering from one of the recited maladies, including HIV infection. Claim 19 further limits the patient group to individuals with a history of substance abuse. Dieterich discloses that patients undergoing IFN- α therapy can have HIV or use drugs intravenously. *See* Dieterich, S128, second paragraph.

Regarding the "neuropsychiatric effects" of IFN- α therapy, the reference only lists anxiety, depression, irritability, emotional lability, suicidal ideation, sleep disturbance, personality change, memory impairment, agitation, and fatigue. *See* Dieterich, S134, first and fourth paragraphs. These psychiatric symptoms are distinct from psychosis. And as explained above, a skilled artisan would also not understand the broad term "neuropsychiatric effects" as automatically inclusive of psychotic symptoms.

The patent publications cited above demonstrate the knowledge that psychotic side effects resulting from IFN- α can arise in a small subpopulation of patients. However, the Examiner still provides no reason a person of skill would expect the methods of Schatzberg, which are aimed at ameliorating psychotic symptoms arising from glucocorticoid dysregulation, to have any effect on the side effects of IFN- α therapy. Dieterich does not provide any more of a link between glucocorticoid regulation and IFN- α therapy than do Schatzberg or Ademmer. For these reasons, Applicants respectfully request withdrawal of the rejection under 35 USC § 103.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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